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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,996	KEATING ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *5,15-21,25 and 40-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14, 22-24, 26-39 and 48-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 4-1-04 has been entered. Claims 1, 48 and 49 have been amended. Claims 60-73 have been added. Claims 1-73 are pending. Claims 1-4, 6-14, 22-24, 26-39 and 48-73 are under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4, 6-14, 22-24, 26-39 and 48-59 remain rejected and claims 60-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a tropoelastin or 7 repeats of the heameric sequence derived from human elastin, i.e. SEQ ID No. 2, or comprising a polypeptide having amino acid sequence that is at least 95% identical to the sequence of SEQ ID No. 3, or a method for preventing vascular restenosis by using said composition *in vitro* or via direct administration of said composition to a targeted site *in vivo*, does not reasonably provide enablement for a pharmaceutical composition comprising a polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID No. 3, or comprising a bioactive fragment of SEQ ID No. 3 including one to seven repeats of a hexameric sequence represented by SEQ ID No. 1, or comprising a peptide fragment consisting essentially of one to seven repeates of the hexameric sequence of SEQ ID No. 1, and a method for prophylaxis or treatment of a disorder having diminished capacity to regulate smooth muscle cell function, including vascular stenosis, obstructive vascular disease, stenosis and restenosis,

by delivering said pharmaceutical composition to a targeted site via any administration route *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 9-30-03 (Paper No. 17). Applicant's arguments filed 4-1-04 have been fully considered but they are not persuasive.

The newly added claims 60-73 are directed to a pharmaceutical composition that provides an elastin-based composition comprising, or consisting essentially of, a polypeptide consists essentially of (i) an amino acid that is at least 90% or 95% identical to SEQ ID No. 3, (ii) a bioactive fragment of SEQ ID No. 3 including one to seven repeats of the hexameric sequence of SEQ ID No. 1, or (iii) a peptide fragment consisting essentially of one to seven repeats of the hexameric sequence of SEQ ID No. 1, wherein said elastin-based composition is attached to a biocompatible support or dissolved in a biocompatible matrix and has one or more biological activity selected from the group consisting of a) inhibiting the proliferation of smooth muscle cells; b) stimulating the differentiation of smooth muscle cells; c) regulating the migration of smooth muscle cells; and d) binding to smooth muscle cells, and said elastin-based composition has an IC50/EC50 for at least one of said biological activities that is less than or equal to 10^{-3}.

Applicants cite examples 6-7, pages 56-58, and argue that the specification provides working example of an elastin-based composition on a biocompatible support and delivered into the artery of an animal. Applicants further argue that the claimed compositions are formulated in association with a biocompatible support and delivered to target site and the claims are directed to particular routes of administration (amendment, page 14-15). This is not found persuasive

because of the reasons set forth in the preceding Official action mailed 9-30-03 (Paper No. 17). Although the rejection under the ground of administration routes in vivo does not apply to the claims that are directed to pharmaceutical compositions, however, it does apply to the method claims including claims 22-24, 26-32, 35-39 and 51-55. The specification only teaches delivery of a peptide having the sequence of SEQ ID No. 2, which has 7 repeats of hexamer derived from human elastin, or elastin tube to coronary artery by direct administration of said peptide or elastin tube into the coronary artery via the use of intravescular stent and balloon catheter (see specification pages 56-58). The claims read on using the pharmaceutical composition to prevent or treat various disorders as claimed via various administration routes *in vivo*. The claims are not limited to a particular administration route. The specification fails to provide adequate guidance and evidence that the claimed polypeptides could be used for prophylaxis or treatment of disease or disorders, such as atherosclerosis, restenosis, vascular bypass graft stenosis, transplant arteriopathy, aneurysm and dissection etc., so as to provide therapeutic effect in treating or preventing said diseases or disorders via various administration routes *in vivo*. Administration route of a pharmaceutical composition plays an important role in the efficiency of said composition *in vivo*. The type of administration route determines how the claimed elastin-based composition reaches its targeted site *in vivo*. The location of administration, the amount and stability of the polypeptides or peptides *in vivo*, and its compartmentalization within the cell are all important factors in determining whether sufficient polypeptides or peptides can reach their target site so as to provide therapeutic effects for preventing or treating diseases or disorders as set forth above *in vivo*.

Applicants cite page 17, line 14 to page 20, line 23, and page 22, lines 5-12 of the specification and argue that the specification teaches the making and testing of variant elastin-based composition as well as fragments of elastin-based compositions. Applicants further argue that the art of combinatorial chemistry allows the making and testing of polypeptide variants without undue experimentation and one skilled in the art can make and test the polypeptide variants without undue experimentation (amendment, p. 16). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-30-03 (Paper No. 17). The state of the art of elastin shows that different elastin or tropoelastin derived from different organisms can have different types of repeat that might contribute to the biological function of elastin or tropoelastin. It is unclear whether the VGVAPG repeat and how many VGVAPG repeat is the structural feature required for the biological activities of elastin or tropoelastin. Elastin peptide VPGVG stimulates the proliferation of chick vascular smooth muscle cells, which is contrary to the disclosed biological activity of inhibiting proliferation of smooth muscle cells of the claimed polypeptides. Both monomer and polymer of VGVAPG enhanced cell proliferation of fibroblast cells, however, both monomer and polymer of VPGVG do not. Polypeptides or peptides comprising at least one hexameric sequence of SEQ ID No. 1 encompasses adding unknown amino acid sequences to 5' and/or 3'end of SEQ ID No. 1 and those unknown sequence may affect or alter the biological function of SEQ ID No. 1. Further, protein function is unpredictable from mere amino acid sequence, it would be unpredictable whether a polypeptide comprising or consists essentially of (i) an amino acid that is at least 90% identical to SEQ ID No. 3, (ii) a bioactive fragment of SEQ ID No. 3 including one to seven repeats of the hexameric sequence of SEQ ID No. 1, or (iii) a peptide fragment consisting essentially of one to seven repeats of the hexameric sequence of SEQ ID No. 1 would have the claimed biological functions. Although one skilled in the art may be able to make those polypeptide variants without undue experimentation, however, determining the biological

functions of the full scope of the claimed polypeptide variants would require undue experimentation for one skilled in the art at the time of the invention because of the unpredictable nature of the biological function of a protein from mere amino acid sequence.

Applicants argue that one skilled in the art could readily make and test polypeptide variants that retain the function properties of tropoelastin, and the specification demonstrates that the human tropoelastin protein retain functional activity in mouse cells and in rabbit system. Applicants argue that tropoelastin is amenable to changes in amino acid sequence because tropoelastin from a particular species retains its functional activity when administered in vitro or in vivo to cells or tissues from another species (amendment, p. 17, 18). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-30-03 (Paper No. 17) and the reasons set forth above. Human tropoelastin can function in mouse cells or rabbit cells only shows that the human tropoelastin can function in different biological environment but does not mean that polypeptide variants of the human tropoelastin would have the same biological function of the human tropoelastin. Protein function is still unpredictable from mere amino acid sequence at the time of the invention.

Applicants cite Dr. Dean Li's declaration and argue that peptide VGVAPG retains the functional activity of tropoelastin when assayed in an in vitro system and tropoelastin comprising seven repeats of the hexameric sequence represented in SEQ ID No. 1 function in vivo, therefore, VGVAPG would function in vivo (amendment, p. 19). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-30-03 (Paper No. 17) and the reasons set forth above. Although Dr. Li's declaration shows the function of peptide VGVAPG on smooth muscle cells in vitro, the claimed invention cites "pharmaceutical composition" and is directed to the use of a peptide or polypeptide comprising VGVAPG so as to provide therapeutic effects in vivo. In vitro environment differs dramatically from the in vivo environment and the *in vitro* data cannot be extrapolated into success in *in vivo* environment.

Further, the claims encompass using the claimed polypeptides or peptides to treat or prevent various diseases or disorders via various administration routes in vivo but the specification fails to provide sufficient enabling disclosure for those uses of the claimed polypeptides or peptides via various administration routes in vivo. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed. Therefore, claims 1-4, 6-14, 22-24, 26-39 and 48-59 remain rejected and claims 60-73 are rejected under 35 U.S.C. 112 first paragraph.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

S Chen